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GB A 2077102 US 3919424
GB 1298771 US 3801631
US 4138581 US 3341584
US 3993776
D. L. Temple at al Journal of Medicinal Chemistry Vol 19 No 5 pgs 626-663 (1976)

(58) Field of search
A5B

# (54) Anti-inflammatory $B_2$ agonists

(57) A topical anti-inflammatory effect in mammals is obtained with particular $B_2$ agonists. The compositions can be for example in the form of sprays, ointments, creams, gels, lotions, and suppositories, all of which are to be applied to the mammal topically, especially phenetharolamines e.g. zinterol, azazinterol and bitolxerol. Also, N-(3-indolyl-isopropyl)- and N-(3-indolyl-*t*-butyl)-2-(4-hydroxy-3-methanesulfonamidophenyl)-2-hydroxyethylamines and their pharmaceutically acceptable salts are antiasthmatic agents as demonstrated by bronchodilation action and inhibition of smooth muscle contraction caused by antigen-induced release of chemical mediators.

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SPECIFICATION

**Phenethanolamines and uses thereof**

This invention relates generally to anti-inflammatory, topically applied nonsteroidal compositions and to their uses and relates more specifically to such compositions having as active ingredient $\beta_2$-adrenergic agonist(s).

This invention also relates to heterocyclic carbon compounds of the indole series having an amino substituent and relates to drug bio-affecting and body-treating processes employing these compounds.

Applicants emphasize that although there are at least hundreds (perhaps thousands) of $\beta_2$-agonists known in the art, only salbutamol has been disclosed as having any topical anti-inflammatory activity. It is believed that no structure-to-activity relationship for predicting topical anti-inflammatory activity is known in the art at this time. The art area is very unpredictable.

Inflammation is exhibited by most skin diseases. A variety of inflammatory skin diseases and conditions (including chronic and acute types) has resulted in an ongoing search for anti-inflammatory drugs.

The introduction of steroids provided the dermatologist with a class of anti-inflammatory agents that are therapeutically active against a wide spectrum of inflammatory skin diseases. However, the effect of steroids in many inflammatory conditions, particularly in those of a chronic nature, is only palliative and requires extended use. And such extended use of steroids also results in various adverse effects, including atrophy of skin, striae, telangiectasia, steroid acne, and adrenal suppression, especially in children. Additionally, in various chronic inflammatory skin diseases, the termination of steroid therapy has led to the reappearance of inflammatory symptoms and sometimes with increased intensity. In response to the drawbacks of using steroids, over the last 20 years many new nonsteroidal anti-inflammatory agents (i.e., NSAIA) have been developed for use in various diseases, including rheumatic diseases. These compounds generally appear to be free of some of the adverse effects of steroids, especially tissue atrophy, adrenal suppression, and other less severe rebound effects.

One class of compounds included within the group of NSAIA is a group of compounds that are prostaglandin synthetase inhibitors. These materials are generally active in reducing UVB-induced erythema (i.e., erythema induced by ultraviolet light) in guinea pigs; but the materials are only slightly active or are inactive in other tests relating to dermatitis, including the croton oil and the oxazolone ear edema assays further described in the examples below. Therefore, other classes of nonsteroidal compounds with topical anti-inflammatory activity are of interest.

$\beta$ adrenergic agonists (including $\beta_1$ and $\beta_2$ agonists) are compounds which have been proposed to act through the stimulation of adenylate cyclase, resulting in the conversion of adenosine triphosphate (i.e., ATP) to cyclic 3',5',-adenosine monophosphate (i.e., C-AMP). See, for example, *R. J. Brittain, et al, Adv. Drug Res. 5*, 197, 1970. The walls of essentially all nucleated mammalian cells contain the enzyme adenylate cyclase, which is stimulated by various compounds including prostaglandin E and $\beta$-adrenergic drugs.

Adenylate cyclase activity has been reported to be present in human and animal epidermis. Disorders in adenylate cyclase activity and in C-AMP levels have been reported in proliferative skin diseases such as eczema, psoriasis, epidermolytic hyperkeratosis and lamellar ichthyosis.

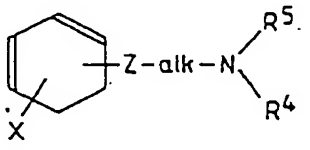
In short, $\beta$ agonists are a class of compounds which stimulate the adrenergic system of the human body.

Materials which are classified as $\beta_1$ agonists are $\beta$ agonists which selectively react with the $\beta_1$ receptors and elicit cardiac stimulation.

Materials which are classified as $\beta_2$ agonists selectively react with the $\beta_2$ receptors which are present in the smooth muscles of the blood vessels and bronchi; these materials elicit bronchodilation and vasodilation.

In British Patent 4,323,575 to G. Jones, April 6, 1982, disubstituted catecholamines (which may or may not be $\beta_2$ agonists) having topical anti-inflammatory activity are disclosed.

In U.S. Patent 3,341,584 to Larsen et al sulfonanilides having the general formula I are disclosed.




formula I

As disclosed in that patent, the sulfonanilides of formula I, wherein Z is CHOH, are pharmacologically active phenethanolamines having actions which either resemble the effects of the adrenal medullary hormones or adrenergic neurotransmitters or oppose the effects of the adrenal medullary hormones or adrenergic neurotransmitters. Alkyl and aryl-sulfonamido nuclearly substituted phenalkanolamines have useful pharmacologic effects, suiting them variously as vasopressors, vasodepressors, analgesics, bronchodilators, $\alpha$-receptor stimulants, $\beta$-receptor stimulants, $\alpha$-receptor blocking agents, $\beta$-receptor blocking agents, papaverine-like smooth muscle depressants, or anti-inflammatory agents useful in controlling or preventing anaphylaxis.

Anaphylaxis is defined in the *McGraw-Hill Dictionary of Scientific and Technical Terms*, Second Edition, 1978, as hypersensitivity following parenteral injection of an antigen, wherein local or systemic allergenic reaction occurs when the antigen is reintroduced after a time lapse. Topical is defined to be "local or designed for local application" and that term is so used in this application. Therefore, because anaphylaxis and topical inflammations are different conditions physiologically, a drug which is useful in treating one of these conditions is generally not useful in treating the other condition.

In U.S. Patent 3,801,631, to Comer et al., patented April 2, 1974, 2-hydroxy-5'-[1-hydroxy-2-(2-methyl-1-phenyl-2-propylamino)ethyl]methanesulfonanilide, called zinterol (which is included within the broad genus of sulfonic acid amides disclosed in U.S. Patent No. 3,341,584 cited above) is disclosed. Zinterol was there described as a potent anorexigenic agent, as an orally active bronchodilator, and as having analgesic activity.

In the article "Adrenergic Sulfonanilides. 4. Centrally Active β-Adrenergic Agonists", D. L. Temple et al, *Journal of Medicinal Chemistry*, Vol. 19, No. 5, Pgs. 626-633 (1976), zinterol (compound No. 43) is described as a potent anorexiant and as a narcotic antagonist.

Additionally, in U.S. Patent 3,919,424 and in U.S. Patent 3,993,776, further description of the uses of zinterol is given.

Salbutamol is a $\beta_2$ agonist. This material was described in *R. Seely et al, Proc. Soc. Exp. Biol. Med. 159*, 223 (1978) as being useful as a topical anti-inflammatory agent.

The synthesis of salbutamol is described in *Drugs of the Future* IV, 629 (1979). There, salbutamol is indicated as being useful as an anti-inflammatory agent when applied locally. It is further stated that salbutamol given orally in the control of asthma compares favorably with related drugs. A mechanism for the action of salbutamol is proposed. (See page 631 of the reference.)

A 1980 publication by Saiichirou Seo et al, "Inhibition of Adjuvant Arthritis by Salbutamol and Aminophylline," European J. of Pharmacology, 63, 267-274, 1980, describes inhibition of swelling in the paws of mice by injections of combinations of salbutamol and aminophylline.

Other materials showing some structural similarity to zinterol and having topical anti-inflammatory activity are disclosed in U.S. Patent 4,323,575 to Jones. These materials may or may not be β-agonists and only testing would determine whether they are.

In U.S. Patent 4,088,756 to Voorhees, other ®-agonists which may or may not have anti-inflammatory activity are disclosed.

However, as further described below, which $\beta_2$-agonists will be effective topical anti-inflammatory agents cannot be predicted with any reasonable degree of certainty. After much experimentation, applicants found that nearly all $\beta_2$ agonists they tested for such activity were either ineffective, highly toxic, or both.

Therefore, despite what has been known in the prior art, there is a continuing need for non-steroidal anti-inflammatory drugs which exhibit consistently good anti-inflammatory activity and which are nontoxic.

A very large body of prior art exists for β-adrenergic agonist compounds of the catechol-type phenethanolamine series.

Larsen, et al., U.S. Patent 3,341,584 cited above broadly disclosed catechol type phenethanolamines wherein one of the phenyl ring hydroxy groups was replaced with sulfonic acid amido thereby giving compounds with β-adrenergic biological acitivity.

Robinson, U.S. Patent 2,908,691, patented October 13, 1959, disclosed a broad group of hydroxy-phenalkylaminoalkylindoles specifically described as having various effects on the central nervous system as well as acting as antisecretory agents, effective in reducing gastric acidity. The most relevant compound of this reference would seem to be 3-(2-[2-hydroxy-2-(3,4-dihydroxyphenyl)ethylamino]propyl)indole tartrate. This compound was prepared as Example 7 in the reference.

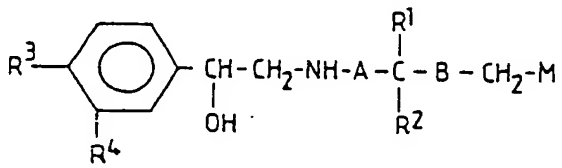
An object of this invention is a material which when placed into a suitable vehicle provides a composition which when topically applied reduces the amount of topical inflammation of a mammal.

Another object of this invention is a composition in the form of an ointment, cream, lotion or other formulation to be topically applied to a mammal so as to reduce or hinder the development of skin inflammation.

A further object of this invention is a method of using a compound (or compounds, in a mixture) for the purpose of reducing topical inflammation of mammals.

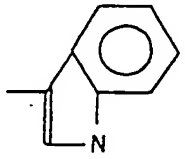
The above-described objects are satisfied by the compositions of the present invention, which comprise:

(a) An amount effective to produce a topical anti-inflammatory effect of at least one compound (or pharmaceutically acceptable salt(s) or solvate(s) thereof) selected from the group consisting of compounds having the general formula II



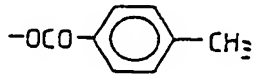
II

wherein $R^1$ and $R^2$ are independently H or a lower alkyl group, provided that $R^1$ and $R^2$ cannot both be H, M is either H, a phenyl group, or an indole group of formula (a)

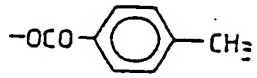


(a)

A is $(-CH_2-)_n$ in which n is the integer 0, 1, or 2, and B is $(-CH_2)_m$ in which m is the integer 0, 1, or 2, $R^3$ is either -OH or



and $R^4$ is either $-NH-SO_2-CH_3$ or



and

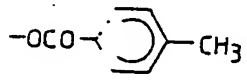
(b) A dermatologically acceptable carrier therefor.

In a preferred aspect of the invention, $R^1$ and $R^2$ are both methyl groups and m and n are both 0. A preferred compound for use in the methods and compositions of the invention is the compound of formula II wherein n is 0, m is 0, $R_1$ is $-CH_3$, $R^2$ is $-CH_3$, M is phenyl, $R^3$ is -OH, and $R^4$ is $-NH-SO_2-CH_3$. This compund is known as zinterol (referred to hereinafter as compound III).

Another preferred compound for use in the methods and compositions of the invention is the compound of formula II wherein n is 0, m is 0, $R^1$ is $-CH_3$, $R^2$ is H, M is an indole group, $R^3$ is -OH, and $R^4$ is $-NH-SO_2-CH_3$, which compound is hereinafter referred to as Compound IV.

Yet another preferred compound for use in the methods and compositions of the invention is the compound of formula II wherein n is 0, m is 0, $R^1$ and $R^2$ are both $-CH_3$, M is an indole group, $R^3$ is -OH, and $R^4$ is $-NH-SO_2-CH_3$, which compound is hereinafter referred to as Compound V or azazinterol.

A still further preferred compound for use in the methods and compositions of the invention is the compound of formula II wherein n is 0, m is 0, $R^1$ and $R^2$ are both $-CH_3$, M is hydrogen, and $R^3$ and $R^4$ are both



That compound is hereinafter referred to as bitolterol and is commercially available for use in treating allergies but has not been known previously to be useful for treating topical inflammations.

In another aspect of the invention, a method for reducing topical inflammation in mammals comprises: applying a compound of formula II topically to the mammal so that *localized* (as opposed to systemic) activity against topical inflammation results.

Further according to the invention, a composition to be topically applied to reduce the amount of topical inflammation of mammals comprises at least one compound of formula II present in a nontoxic amount sufficient to reduce inflammation and present in a pharmaceutically acceptable carrier material or materials, wherein A, B, $R^1$, $R^2$, $R^3$, $R^4$ and M are as described above.

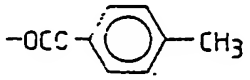
In another preferred aspect of the invention, a composition to be topically applied comprises at least one compound selected from the group consisting of zinterol, compound IV, compound V, and bitolterol, at least one compound of which is present in an amount sufficient to reduce inflammation but insufficient to be toxic and present in a pharmaceutically acceptable carrier.

It is emphasized that the term "topical" as used throughout this document means local or designed for local application to produce a local effect with preferably no concomitant systemic effect. Thus, the compounds to be used in the methods and compositions of the invention can be applied in any of a variety of ways, provided that they are not injected or swallowed. They can be applied, for example, cutaneously, nasally, vaginally, rectally, optically, and buccally. They will be used with a dermatogically acceptable vehicle preferably chosen such that systemic absorption of the active ingredient is hindered or reduced.

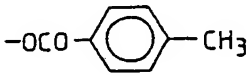
This invention also concerns antiasthmatic agents which are bronchodilators and potent yet selective inhibitors of smooth muscle contraction. The potencies and selectivities of these agents in inhibiting smooth muscle contraction caused by antigen-induced release of chemical mediators has been demonstrated in pharmacological tests utilizing immunized guinea pig tracheal rings. These agents include compound IV and

compound V and their pharmaceutically acceptable solvates and salts thereof, and the invention includes their utilization as antiasthmatic agents.

The compound(s) which are to be placed into a vehicle so as to provide a composition(s) suitable for topical use as an anti-inflammatory preparation(s) in mammals are the compounds of formula II, recited above, (or pharmaceutically acceptable salts and solvates thereof), wherein M is either a phenyl group, or an indole group or hydrogen, wherein A is $(-CH_2-)_n$ and wherein n equals 0, 1, or 2; wherein B is $(-CH_2)_m$ and wherein m is 0, 1, or 2; wherein $R^1$ and $R^2$ are independently H or a lower alkyl group, provided that $R^1$ and $R^2$ cannot both be H; wherein $R^3$ is either -OH or



and wherein $R^4$ is either $-NH-SO_2-CH_3$ or



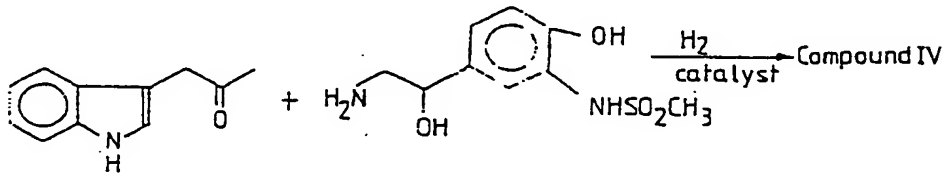
Applicants wish to emphasize that they tested many $\beta_2$ adrenergic agonists (all of which are analogs of zinterol). Of approximately 45 such compounds, only four had consistently high topical anti-inflammatory activity without apparent toxicity in tests which are described in the examples below. The remainder of the compounds, on the other hand, exhibited either toxicity when applied topically to the test animals, ineffective and/or inconsistent anti-inflammatory activity, or both.

The compound(s) to be placed into a vehicle so as to provide a composition suitable for topical use as an anti-inflammatory preparation in mammals are prepared in the following manner.

The preparation of zinterol is described in detail in U.S. Patent No. 3,801,631 to William T. Comer et al, "2'-hydroxy-5'-[1-hydroxy-2-(2-methyl-1-phenyl-2-propylamino)ethyl]methanesulfonanilide and its Salts"; and that patent is hereby incorporated herein by reference.

As used herein, Me stands for a methyl group. A detailed description of the preparation of compounds IV and V is the following. Compound IV and V can be prepared by selecting from two general methods. The first synthetic method shown hereinafter,

*Method 1*

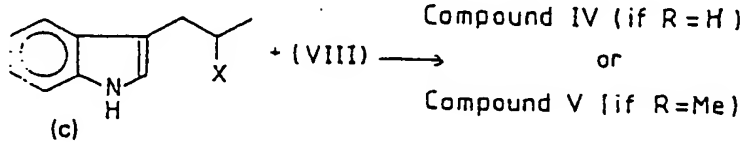



(b) VIII

involves reductive amination of an indolylcarbonyl compound with an appropriate phenethanolamine. Choice of reagents and conditions for reductive aminations are well known to those skilled in the art. In general, the reaction is carried out by shaking a solution of the appropriate carbonyl compound and phenolic amine in a solvent such as a lower alkanol, e.g. methanol, in the presence of a hydrogenation catalyst, e.g. a noble metal catalyst such as platinum oxide, in a hydrogen atmosphere. As an alternative, the reaction could also be carried out stepwise by first forming the condensation product of the carbonyl compound and the phenolic amine and then conducting the hydrogenation as a separate operation.

A variation of synthetic method 1 entails nucleophilic displacement by the phenolic amine on an indolylalkyl halide or an equivalent. This is shown below as Method 1A.

*Method 1A*

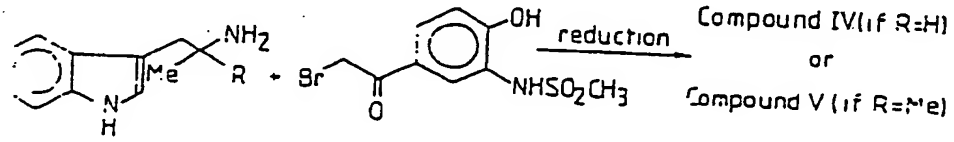



(c)

wherein X is a typical leaving group such as halide, tosylate, etc. Again, choice of reaction conditions and reagents for nucleophilic displacement reactions are well known and would be familiar to one practiced in the chemical arts.

The second process which can be used for preparation of compound IV or compound V is shown below as general synthetic method 2. This general method can also be used for the preparation of compound V as shown.

*Method 2*

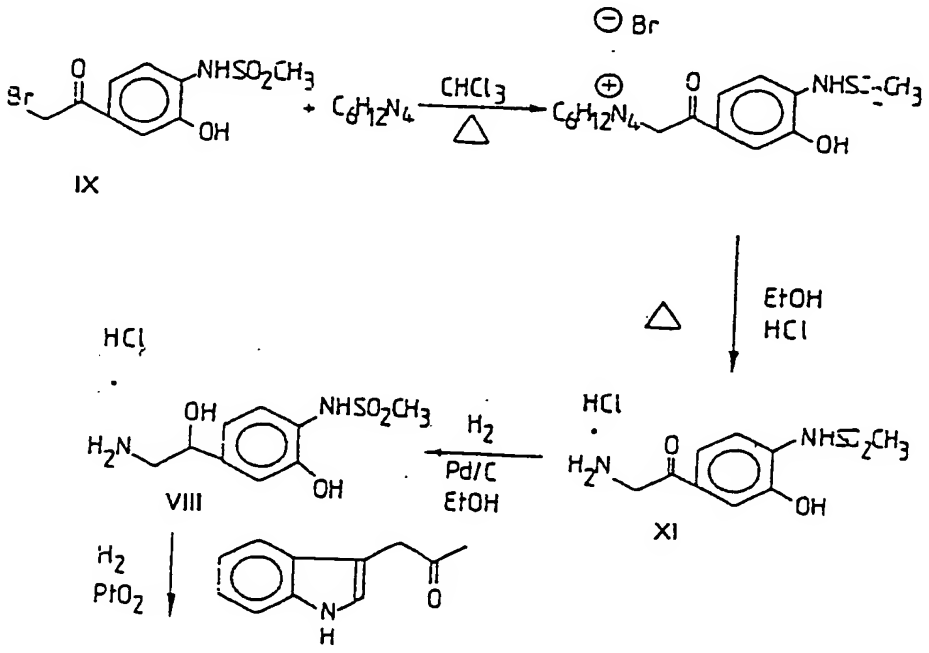


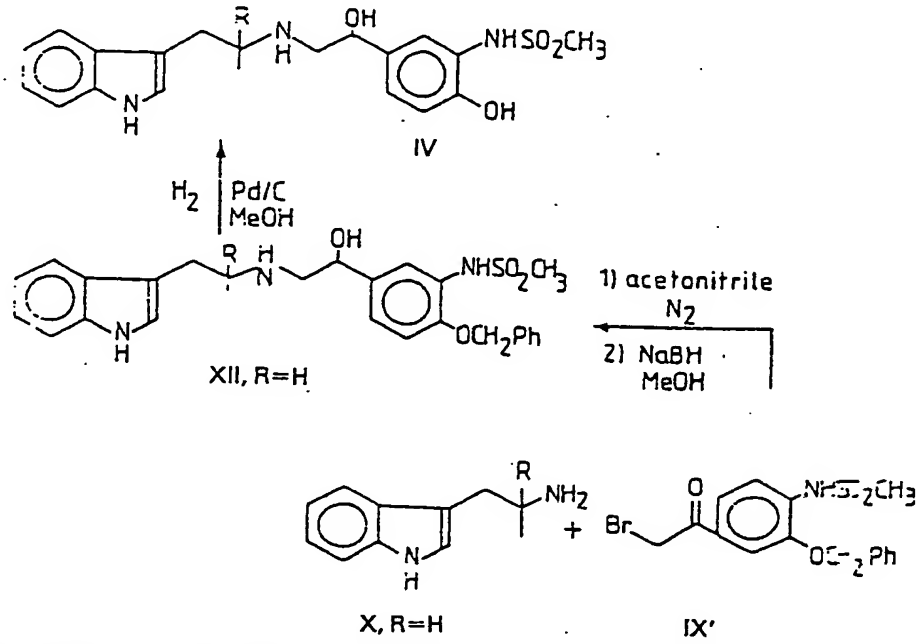

(X) (IX) (IX)

This process comprises alkylation of the phenolic bromoketone by the appropriate indolylalkylamine followed by reduction of the carbonyl group to a secondary alcohol. In practice, the phenolic OH group is protected during the nucleophilic displacement reaction. This is done to prevent participation by the phenolic group in nucleophilic attack of its own thereby giving unwanted ether byproducts. Generally, the protection is done *via* a benzyl group which is subsequently removed by catalytic reduction.

These general synthetic methods have been incorporated into the actual synthetic schemes used to produce compounds IV and V. These specific schemes are outlined below.

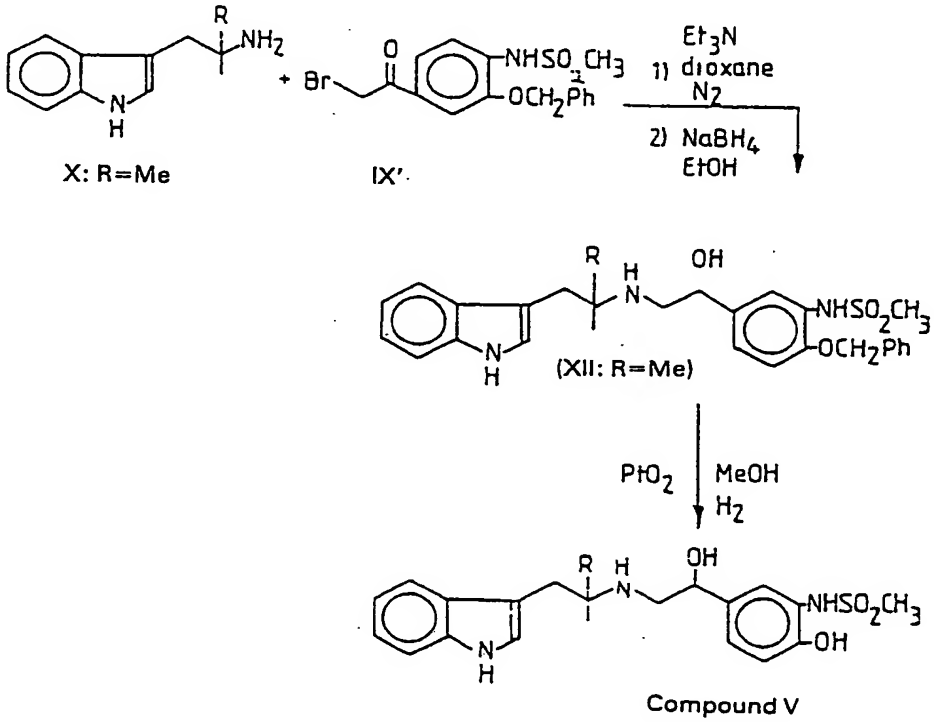
Scheme A: Preparation of Compound IV






Scheme A outlines the preparation of compound IV. Two pathways are depicted, both beginning with one of the bromoketones, IX and IX'. In the upper pathway IX is reacted with hexamethylenetetramine ($C_6H_{12}N_4$) to yield a quaternary salt which is converted to the aminoketone XI followed by catalytic hydrogenation to the phenethanolamine VIII. Reductive alkylation of 3-indolylacetone with VIII affords the subject compound IV as shown. The lower and preferred pathway proceeds *via* nucleophilic attack of the indolylamine X or IX' (the O-benzyl analog of IX) followed by borohydride reduction to give the benzyl-blocked phenolic group intermediate (XII: R=H) as shown which is in turn catalytically reduced to the desired end product.

Scheme B: Preparation of Compound V




Scheme B depicts the preparation of compound V utilizing essentially the same pathway as shown in the lower part of Scheme A above. In Scheme B the appropriate indolylamine is reacted with IX', and the resulting adduct is reduced with borohydride to give the protected phenolic compound (XII: R=Me) as shown which is then converted *via* catalytic hydrogenation to the desired subject compound compound V.

These two synthetic schemes, *supra.*, will be exemplified in greater detail hereinbelow. Intermediate compounds utilized in these syntheses are either available commercially, e.g. 3-indolyl acetone; or as

described in the chemical literature such as the references cited in the *Background of the Invention* section hereinabove.

The preparation of bitolterol is discussed in U.S. Patent 4,138,581; and that discussion is hereby incorporated herein by reference.

For medicinal use, the pharmaceutically acceptable solvates and salts are those complexes in which the solvent, metal cation or acid anion does not contribute significantly to toxicity or pharmacological activity of the organic drug ion. The sulfonamido group is the acidic function utilized in metal salt formation. Examples of metal salts include the sodium, potassium, calcium, magnesium, aluminum and zinc salts. Metal and acid addition salts are obtained, respectively, either by reaction of the selected compound with a suitable metallic base to form a metal salt or with an organic or inorganic acid to form an acid addition salt, preferably by contact in solution, or by any of the standard methods detailed in the literature and available to any practitioner skilled in the art. Examples of useful organic acids are carboxylic acids such as maleic acid, acetic acid, tartaric acid, propionic acid, fumaric acid, isethionic acid, succinic acic, pamoic acid, cyclamic acid, pavalic acid, and the like. Useful inorganic acids are hydrohalide acids (such as HCl, HBr, HI), sufuric acid, phosphoric acid, and the like.

Solvates as used herein are complexes comprising an organic drug molecule and a solvent moiety of formula ROH, wherein R most commonly is hydrogen or a $C_1$ or $C_4$ alkyl group. The most common solvate is the hydrate.

It is also to be understood that the compounds of the present invention include all the optical isomer forms, that is, mixtures of enantiomers, e.g., racemic modifications as well as the individual enantiomers and diastereomers. The individual optical isomers of the phenethanolamine class of compounds of which the instant compounds are members, have most generally been obtained by one of four basic methods. These are: 1) the fractional recrystallization of chiral acid salt derivatives; 2) derivatization with a chiral organic reagent, resolution, and regeneration of the original compound in optical isomer form; 3) synthesis of the single optical isomer using chiral intermediates; and 4) column chromatography utilizing chiral stationary phases. The application of these various methods are well known to practitioners in the art.

The compounds recited above which are to be placed into a vehicle so as to provide compositions suitable for topical use as anti-inflammatory preparations in mammals can be placed into the following vehicles. The resulting mixtures are pharmaceutical preparations of the invention. The vehicle can be any nontoxic material or mixture of materials which is suitable for use in preparing pharmaceutically acceptable ointments, salves, lotions, sprays, suppositories and other similar medicaments. The vehicle, additionally, will be chosen so that it preferably hinders or reduces systemic absorption of the active material(s) and it should not react with the active ingredient(s) described above. Additionally, the active ingredient(s) should be both soluble in the vehicle and should be released by the vehicle topically. Furthermore, the mixtures so formed will preferably be stable over an extended period of time, for example on the order of months or years.

The active ingredient(s) will generally be dissolved into a component of the vehicle. For example, zinterol hydrochloride is both water soluble and soluble at least to some extent in various organic materials. For topical applications to the skin, because there is both an aqueous phase and a non-aqueous phase in the skin, both water soluble and oil soluble portions of the vehicle will permeate the skin. However, for topical use, one would use some organic phase in the vehicle (for example, petrolatum or mineral oil).

Vehicles for carrying active ingredients into the skin, for example, creams, lotions, gels, ointments, suppositories, and sprays, as well as methods of preparation thereof, are well known in the art. In the present invention, at least one active ingredient will be dissolved in a portion of the vehicle in which it is soluble, and the resulting mixture will then be mixed in any suitable way with the remaining ingredients of the vehicle.

The relative amount of vehicle to be mixed with active ingredient(s) (i.e., with the compounds described above) in forming the mixtures of the invention will be selected depending upon the solubility of the active ingredient(s) in the vehicle. However, it is believed that the optimal concentration is generally the saturation point. For zinterol hydrochloride, however, the optimal concentration thereof in a cream vehicle was found to be 0.2 w/v percent, although up to 0.7 w/v percent thereof will dissolve in creams.

The mixtures of the invention will be administered in the following way. Based upon the tests described in the examples below, the mixtures of the invention prepared from active ingredient(s) in suitable vehicle should be applied as soon as possible after the skin has come into contact with the material(s) that caused the inflammation being treated.

The mixtures of the invention will be applied directly to the area of inflammation to produce a localized effect. Although in salbutamol (discussed above) a systemic effect was noted, none was found in preliminary tests done on the materials used in this invention. It is an advantage to have no systemic effect and to have minimal absorption of these materials.

Additionally, biological testing of compounds IV and V demonstrates that they posses intrinsic bronchodilator action and they are able to reverse antigen-induced tracheal contraction. This contractile response to antigen has been characterized as consisting of an initial spasm caused by release of preformed histamine followed by a sustained contraction due to the release of newly synthesized SRS-A (slow reacting substance of anphylaxis) (cf: Brocklehurst: The Release of Histamine and Formation of a Slow-Reacting Substance (SRS-A) During Anaphylactic Shock, *Journal Physiology*, 151:416-435, 1960). The ability of the subject compounds to inhibit the contractile response mediated by SRS-A with significantly greater

inhibitory potency compared with the released histamine contractile response demonstrates an advantage in *selectivity* for the subject compounds which would make them particularly useful as antiasthmatic agents. The utility of compounds IV and V in this regard can be demonstrated in various pharmacologial tests which include inhibition of methacholine-induced bronchospasm in rats, and inhibition of smooth muscle contraction caused by antigen-induced release of chemical mediators in tracheal rings isolated from immunized guinea pigs. This latter method has been adapted from Adams and Lichtenstein: *In Vitro* Studies of Antigen-induced Bronchospasm: Effective Antihistamine and SRS-A Antagonist on Response of Sensitized Guinea Pig and Human Airways to Antigen. *Journal of Immunol.*, 122:555-562, (1979).

For use as antiasthmatics, therapeutic processes of this invention comprise systemic administration, by both oral and parenteral routes as well as by inhalation of an effective, nontoxic amount of compound IV or compound V or a pharmaceutically acceptable salt thereof. An effective amount is construed to mean a dose which exerts the desired pharmacological activity, such as those stated hereinabove without undue toxic side effects when administered to a mammal in need of such treatment. Dosage will vary, according to the subject and route of administration selected, with an expected range of about 0.1 mcg to 100 mg/kg body weight of a compound of Formula IV or V or a pharmaceutical acceptable acid addition salt thereof generally providing the desired therapeutic effect.

Compounds IV and V can be formulated according to conventional pharmaceutical practice to provide pharmaceutical compositions of unit dosage form comprising, for example, tablets, capsules, powders, granules, emulsions, suspensions, and the like. These preparations contain the active ingredient, usually in admixture with nontoxic pharmaceutical excipients, to give solid dosage forms or as a solution, suspension, or emulsion to give a liquid preparation. It is understood that other standard pharmaceutical practices also apply such as the addition of sweetening and flavoring agents or use of binders, etc. Further, the compositions may also contain other absorbing agents, stabilizing agents, wetting agents and buffers.

Additionally, liquid preparations of compounds IV and V may be used for administration by inhalation given, for example, by nebulization. The instant compounds can also be administered as a powder for insufflation, consisting of a blend of inert powder ingredients admixed with an appropriate amount of the instant compound of appropriate particle size, administered by a powder insufflation device. Generally, one part micronized drug is blended with 50 parts USP lactose having appropriate microbial properties. This blend is encapsulated for use in a suitable insufflation device. Prior to use, the capsule must be punctured or opened to allow release of the powder blend.

*Examples*

In examples 1-4, the following types of tests (i.e., models) on animals were used. These were (1) croton oil-induced ear edema in mice, (2) oxazolone-induced ear edema in mice, and (3) UVB-induced erythema in guinea pigs.

*Example 1*

In the croton oil assay, (which is a standard test, which is fully described in Tonelli et al., *Endocrinology*, vol. 77, pp. 625-634, 1965, and which is hereby incorporated herein by reference) topical application of four % croton oil in ethanol (v/v) to the ears of mice causes intercellular edema, vasodilation, and polymorphonuclear leucocyte infiltration into the dermis, leading to an increase over normal ear weight of about 70 to 100%. The inflammatory response is nearly maximal by 6 hours. In the croton oil tests, four volume % croton oil in ethanol was applied to the inner aspect of both ears of each test mouse, and various test materials in vehicle systems were applied to the outer aspect of the ears immediately following croton oil application. Control animals were exposed either to croton oil alone or to croton oil followed by the vehicle alone.

Six hours after exposure to croton oil and/or test material, animals were sacrificed; and punch biopsies of the ears were weighed and compared to the respective vehicle control.

Compounds were tested in simple solutions, including dimethylacetamide/acetone/ethanol/ (i.e., DMAC/A/E v/v 40/30/30) and N-methyl pyrrolidone/ethanol (NMP/E v/v 50/50). Comparative controls were chosen based on their known activity in each of the three above-described animal assays and included in all three tests (in Examples 1, 2 and 3) hydrocortisone valerate (HCV) in the croton oil and oxazolone assays, indomethacin (which is a potent aspirin-like nonsteroidal anti-inflammatory agent) in the UVB test, and salbutamol (a $\beta_2$ agonist, discussed above in the Background of the Invention).

The percent inhibition of induced mouse ear edema (or erythema) for each of the three models (in Examples 1, 2 and 3) is calculated:

$$\frac{\text{Control Ear Weight} - \text{Test Ear Weight}}{\text{Control Ear Weight}} \times 100$$

The croton oil assay appeared to be more sensitive to steroidal anti-inflammatory agents than to aspirin-like nonsteroidal anti-inflammatory agents. Unexpectedly, unlike the aspirin-like nonsteroidal anti-inflammatory agents, the $\beta_2$-agonists used in this invention were effective in reducing the croton oil-induced inflammation.

The anti-inflammatory activities of approximately 45 $\beta_2$-adrenergic agonists were evaluated in the croton

oil-induced mouse ear edema assay (which produces acute dermatitis); and the more active compounds were subsequently tested in the oxazolone-induced mouse ear edema assay (which produces contact allergic dermatitis) and in the UVB-induced erythema assay in guinea pigs.

Out of the group of approximately 45 compounds which included zinterol and analogs thereof, four compounds (one of which was zinterol) demonstrated high topical cutaneous anti-inflammatory activity in the croton oil assay at 1.6 w/v % (weight/total volume ethanol+test material). These four compounds were subsequently tested topically at other concentrations in the croton oil assay and were also tested topically in the oxazolone assay and in the UVB test. In these subsequent tests, zinterol appeared to be the most consistently active compound.

Given below in Table I are the results of zinterol and the controls salbutamol and HCV, at 1.6 w/v% and 0.2 w/v% in the croton oil assay in each of two solvent systems. Also included in Table I is data for bitolterol, a commercially available $\beta_2$ agonist which has previously been used as an anti-allergy compound but which has not previously been known for utility as topically active against cutaneous inflammations. A direct comparison of bitolterol and zinterol was made. Both exhibited similar topical anti-inflammatory activity.

The results in Table I show that in the croton oil assay, zinterol at 1.6 w/v percent and at 0.2 w/v percent and bitolterol at 1.6 w/v percent all showed good to moderate reductions in ear edema and were equivalent to or slightly less effective than hydrocortisone valerate (i.e., HCV) but were more effective than salbutamol.

*Example 2*

Oxazolone-induced contact sensitization in mice is characterized by edema and cellular infiltration, primarily of the monocyte type, with close to 100% increase in the mouse ear weight. (This model is fully described in N. J. Lowe et al., *British J. of Dermatology*, vol. 96, pp. 433-438, 1977, which is hereby incorporated herein by reference. In this model, test materials were applied topically to the outer aspect of the challenged ear of each test animal immediately following the challenge application of oxazolone to the inner aspect of the ear. The animals were sacrificed at 8 or 24 hours after treatment; and punch biopsies of the ears were weighed and compared to controls which were challenged as described above and exposed to the vehicle alone.

TABLE I

*% Inhibition of Croton Oil-Induced Mouse Ear Edema in Two Vehicles*[1]

| *Compound* | *In DMAC/Acetone/ETOH*[2] *1.6 w/v%* | *0.2 w/v%* | *In NMP/ETOH*[3] *1.6 w/v%* | *0.2 w/v%* |
|---|---|---|---|---|
| Zinterol | 69[a], 50[b]<br>81[c], 66[d]<br>63[e], 48[f]<br>45[g] | 54[h],34[i]<br>29[j],6[k]<br>20[l] | 69[m], 63[n]<br>70[o], 48[p]<br>73[q] | 92[r], 58[s]<br>56[t], 44[u]<br>57[v], 38[x]<br>34[y], 61[f] |
| Bitolterol | | | 61 | 42[x], 25[y]<br>34[z] |
| Salbutamol[4] | 26[a], 0[b] | −34[l]*,−45[k] | 54[m], 49[n]<br>23[o], 0[p]<br>37[q] | |
| HCV | 78[c], 59[d]<br>16[e], 48[f]<br>59[g] | 25[j], 38[k]<br>34[l], | 70[n], 71[q] | 71[r], 62[s]<br>64[t], 67[u]<br>73[v] |

1 Each value is the mean of 10 to 15 animals. Approximately 10 to 35% variability is observed in this test.
2 Dimethylacetamide/Acetone/Ethanol (v/v, 40/40/30).
3 N-methyl 2-pyrrolidone/Ethanol (v/v, 50/50).
4 Tested in Ethanol/$H_2O$ (50/50) due to solubility limitations.
[a] to [z] Values with the same alphabetical superscript were observed in the same experiment.
* The minus sign indicates no inhibition, but rather potentiation, of the inflammation.

The oxazolone assay appeared to be sensitive to steroidal anti-inflammatory drugs and relatively insensitive to nonsteroidal anti-inflammatory drugs. Again, unexpectedly, unlike the aspirin-like nonsteroidals (such as indomethacin), the $\beta_2$-agonists showed topical anti-inflammatory activity.

In Table II, the results of tests on percent of inhibition of oxazolone-induced edema in mouse ears using various concentrations of zinterol, salbutamol, or HCV as active ingredient are given for oxazolone in three solvent systems of DMAC/acetone/ethanol (v/v 40:30:30).

From the results in Table II, in the oxazolone assay, one can observe that zinterol at 3 and 1.6 weight

percent showed slight reduction in ear edema with no dose-related effect and was equal to salbutamol but slightly less active than HCV.

Compounds in Tables I and II can be compared directly.

*Example 3*

Another series of tests were run for the sake of completeness, although it was not expected that $\beta_2$-agonists (which are vasodilators) would show results comparable to the aspirin-like nonsteroidal agents (which are not vasodilators). In the UVB test, cutaneous erythema is induced in guinea pigs. This test is a standard test widely used for testing anti-inflammatory agents and is fully described in K. F. Swingle, "Evaluation for Anti-Inflammatory Activity", in *Anti-Inflammatory Agents*, vol. 2, ed, by Scherrer and Whitehouse, pp. 34-122, London: Academic Press, 1974, hereby incorporated herein by refernce. In the UVB model, the test material was applied topically to the irradiated sites immediately following exposure to UVB. Erythema was scored on a 0 to 4 scale, 3 and 6 hours after irradiation.

TABLE II

| *Compound* | *% Inhibition of Oxazolone-Induced Edema in Mouse Ear[1,2] Concentration* | | *% Inhibition of Oxazolone-Induced Edema in Mouse Ear[2,3] Concentration* | |
|---|---|---|---|---|
| | *0.2 w/v%* | *1.6 w/v%* | *1.6 w/v%* | *3 w/v%* |
| Zinterol | 22[a], −17[b] | 48[c], 17[d] 41[e] | 35[h], 30[i] 14[j], 43[k] | 39[l] |
| Salbutamol | −1[a], −9[b] | 2[c], 0[d], | 21[h], 28[i] | 31[l] |
| HCV | 16[a], 16[b] | 36[c], 27[d] | 38[h], 8[i] 31[j], 42[k] | 39[l] |

[1] Above agents tested in DMAC/acetone/ethanol (v/v 40:30:30).
[2] Each value is the mean of 10 to 15 animals. Approximately 20 to 35% variability is observed in this test.
[3] Above agents tested in N-methylpyrrolidone:ethanol (v/v 1:1).
[a] to [l] Values with the same alphabetical superscript were observed in the same experiment.

In Table III, the percent changes in UVB-induced erythema in guinea pigs at 3 and 6 hours after treatment with zinterol are given, along with results of treatment with salbutamol and indomethacin.

As shown by the results in Table III for the UVB assay, zinterol at 3 and 1.6 weight percent showed slight to moderate activity with no consistent dose effect and was highly variable. Similar effects were seen with salbutamol. However, indomethacin at 1 weight percent showed good to very good activity on a consistent basis.

The results given above in Tables I, II and III are summarized below in Table IV.

Based upon the summary in Table IV, one can validly conclude that, at the same concentrations, zinterol appears to be almost as effective as HCV and more effective than salbutamol in the croton oil assay. Therefore, zinterol is a promising candidate for reducing anti-inflammatory activity in humans, based upon the data disclosed above. Zinterol is expected to be devoid of many side effects which are exhibited by the current steroid therapy.

TABLE III

*%Change in UVB - Induced Erythema in Guinea Pig at 3 and 6 Hours after Treatment*[1]

| | *Drug Concentration (%)*[2] | | | | *Drug Concentration (%)*[3] | | | |
|---|---|---|---|---|---|---|---|---|
| | *1.6* | | *3* | | *1.6* | | *3* | |
| | | | | | *Time (Hr.)* | | | |
| *Compound* | *3* | *6* | *3* | *6* | *3* | *6* | *3* | *6* |
| Zinterol | 0 | 13 | | | NT* | 9 | 26 | 48 |
| | 37 | 56 | | | | | 75 | 25 |
| | 9 | 19 | | | | | | |
| | 27 | +9 | | | | | | |
| Salbutamol[4] | 9 | +4 | +39 | +39 | | | 42 | 32 |
| | | | 74 | 71 | | | 45 | 25 |
| Indomethacin | 72 | 43 | | | 100 | 74 | | |
| (1%) | 54 | 48 | | | 93 | 85 | | |
| | 82 | 54 | | | 91 | 87 | | |

[1] All test material applied immediately post-irradiation.
[2] Test material prepared in Dimethyl acetamide/acetone/ethanol (v/v, 40/30/30) and given as w/v%.
[3] Test material prepared in N-methyl 2-pyrrolidone/ethanol (v/v, 50/50) and given as w/v%.
[4] Tested in Ethanol/$H_2O$ (50/50) or NMP/$H_2O$ (50/50) due to solubility limitations.
* Not tested due to solubility limits at 1.6%.

Table IV

*Topical Anti-Inflammatory Activity of Zinterol in 3 Animal Models*

*(Salbutamol, HCV and Indomethacin Tested as Comparative Controls)*

| | *Croton Oil Assay (Edema)* | *Oxazolone Assay (Edema)* | *UV-B Assay (Erythema)* |
|---|---|---|---|
| Zinterol | +++ | + | + |
| Salbutamol | + | + | + |
| HCV | +++ | + | NT[1] |
| Indomethacin | + | + | +++ |

Anti-Inflammatory Activity and (range of % inhibition)
+ = Slight (30-44), ++ = moderate (45-59) and +++ = high (60%) [1]NT = Not tested.

*Example 4*

In further testing, two analogs of zinterol, compounds IV and V, were tested and were found to show anti-inflammatory activity comparable to that of zinterol.

In these tests, the anti-inflammatory effect of these three $\beta_2$ agonists when applied topically to the croton oil-induced ear edema in mice was investigated. In these tests, 50 µl of 4 weight percent croton oil in ethanol was applied to the inner aspects of the right and the left ears of Swiss albino mice, followed immediately by 25 µl of suspensions of 0.02, 0.2, and 0.8 weight percent of compound IV and compound V in N-methylpyrrolidone/Ethyl alcohol (i.e., NMP/ETOH) applied to the outer aspect of each ear. Croton oil treated and nontreated control groups were included. These control groups are included in the data as described hereinbefore.

Six hours later, the animals were sacrificed with $CO_2$ gas, and a 5/16 inch punch biopsy of each ear was taken and weighed immediately.

The anti-inflammatory effects for the test agents were assessed by a comparison of the biopsy weights of the test and control groups.

The results of three studies for various concentrations of test material in NMP/ETOH are given below in Table V and show that both compound IV and compound V are comparable to zinterol in reducing the mouse ear edema.

TABLE V

*% Reduction of Ear Edema Weight as Compared to Control Ears + S.D.*

| *Concentration (%)** | *Compound IV* | *Compound V* | *Zinterol* |
|---|---|---|---|
| 0.02 | 10.6 | 29.9 | 14.2 |
| | 25.6 | | 23.6 |
| Mean ± S.D. | 18.1±10.6 | | 18.9±6.6 |
| 0.2 | 32.9 | 53.5 | 39.5 |
| | 48.7 | | 66.2 |
| | 49.4 | | 46.6 |
| Mean ± S.D. | 43.7±9.3 | | 50.8±13.8 |
| 0.8 | 61.6 | 69.9 | 68.2 |
| | 53.4 | | 56.6 |
| Mean ± S.D. | 57.5±5.8 | | 62.4±8.2 |

* Weight/Volume

Data given on the same line in Tables III and V were obtained in the same experiment, and therefore a direct comparison is shown.

It will be appreciated that the compounds of formula II can be formulated into a wide variety of formulations by standard means well known to those skilled in the art. Such formulations include for example nasal sprays (one spray of which may be prepared, for example, with trichloromonofluoromethane, dichlorodifluoromethane, and oleic acid), rectal suppositories, vaginal suppositories, ointments, creams, gels, and lotions.

The methods of preparation of compounds IV and V and their biological actions will appear more fully from a consideration of the following examples and appended claims which are given for the purpose of illustration only and are not to be construed as limiting the invention in sphere or scope. In the following examples, used to illustrate the foregoing synthetic processes, temperatures are expressed in degrees celcius and melting points are uncorrected. The nuclear magnetic resonance (NMR) spectral characteristics refer to chemical shifts (δ) expressed as parts per million (ppm) versus tetramethylsilane (TMS) as reference standard. The relative area reported for the various shifts and the proton NMR spectral data corresponds to the number of hydrogen atoms of a particular functional type in the molecule. The nature of the shifts as to multiplicity is reported as broad singlet (bs), singlet (s), multiplet (m), or doublet (d). Abbreviations employed are DMSO-$d_6$ (deuterodimethylsulfoxide), $CDCl_3$ (deuterchloroform) and are otherwise conventional. The infrared (IR) spectral descriptions include only absorption wave numbers ($cm^{-1}$) having functional group identification value. The IR determinations were employed using potassium bromide (KBr) as diluent. The elemental analyses are reported as percent by weight.

*Example 5*

*5'-(2-Amino-1-hydroxyethyl)-2'-hydroxy-methanesulfonanilide Hydrochloride (VIII)*

To a stirred solution of hexamethylenetetramine (27.4 g, 0.19 mole) in 650 mL chloroform was added in portions 5'-bromoacetyl-2'-hydroxymethanesulfonanilide ((IX) 40.0 g, 0.13 mole). The resulting suspension was refluxed for 16-18 hrs, cooled to room temperature, and then filtered. The solid obtained was washed with chloroform and dried in air to give 56.6 g (97.3%) of quaternary salt product, m.p. 165-167°.

This solid was dissolved in 400 mL ethanol and treated with 65 mL conc. HCl. Refluxing the resulting solution for several minutes caused the initiation of precipitation in the hot solution. The mixture was chilled to aid in completion of preciptitation. The solid, isolated by filtration, was washed by being stirred in water and refiltered. Recrystallization of this material from methanol-isopropyl ether gave a solid product, 5'-glycyl-2'-hydroxymethanesulfonanilide hydrochloride, m.p. 219-221°.

A portion (7.3 g. 0.026 mole) of this aminoketone hydrochloride and 10% palladium-on-carbon (2.0 g) were suspended in 200 mL of hot 90° ethanol. This warm suspension was reduced by shaking under 60 psi hydrogen on a Parr hydrogenation apparatus. Following 12-14 hrs of shaking, the hydrogenation mixture was removed from the Parr apparatus and the catalyst removed by filtration. The filtrate was concentrated *in vacuo* to a white solid residue which was suspended in an isopropyl alcohol-isopropyl ether medium and refiltered to give a quantitative yield of VIII as the hydrochloride salt, m.p. 179-180° (dec).

*Example 6*

*2'-Hydroxy-5'-(1-hydroxy-2-[3-(3-indolyl)-2-propylamino]ethyl)methanesulfonanilide (Compound IV)*

The hydrochloride salt of VIII (5.65 g., 0.02 mole), prepared above, was converted to the base by suspension in 150 mL of ethanol followed by treatement with 2.0 mL of 10.0 N NaOH added dropwise with stirring. The original solid dissolved with concommitant precipitation of NaCl. The NaCl was removed by filtration and the filtrate was concentrated *in vacuo* to a white solid residue which was dissolved in 100 mL of methanol. A reductive alkylation was carried out by adding glacial acetic acid (1.2 g., 0.02 mole) and

3-indolylacetone (3.5 g, 0.02 mole), diluting the resulting solution to 150 mL with additional ethanol and then adding 0.2 g $PtO_2$. This suspension was hydrogenated under 60 psi hydrogen until hydrogen uptake ceased (approximately 4 hrs). The suspension was removed from the hydrogenation apparatus, filtered, and the filtrate concentrated *in vacuo* to an oily residue which was dissolved in warm methanol treated with several drops of glacial acetic acid. Dilution with ethyl ether and stirring while chilling allowed collection by filtration of a solid which was washed with methanol to given 4.7 g of the acetate salt of compound IV, m.p. 196.5-197° (dec).

This material was dissolved in a minimal amount of hot dimethylformamide, filtered and diluted with an equal amount of water to yield a precipitate which was isolated by filtration giving the free base of compound IV, m.p. 198-199° (dec.)

| | | | | |
|---|---|---|---|---|
| Anal. Calcd. for $C_{20}H_{25}N_3O_4S$; | C, 59.53; | H, 6.24; | N, 10.41; | S, 7.94. |
| Found: | C, 59,96; | H, 6.15; | N, 10.65; | S, 8.05. |

NMR (DMSO-$d_6$): 0.98 (3,m); 2.75 (5,m); 2.93 (3,s); 4.52 (1,m); 6.00 (4,bs); 7.15 (8,m).
IR (KBr): 750, 1125, 1150, 1240, 1280, 1325, 1500, 1610 and 2940 $cm^{-1}$.

*Example 7*

*Alternate Preparation of Compound IV*

A solution of 3-(2-aminopropyl) indole (11.0 g, 0.06 mole) in 730 mL acetonitrile was stirred under a nitrogen atmosphere as 5'-bromoacetyl-2'-benzyloxy-methanesulfonanilide (12.5 g, 0.03 mole) was added in a single portion. After stirring at room temperature for 0.5 hr, a cold solution of sodium borohydride (4.8 g, 0.126 mole) in 219 mL methanol was added at a fast dropwise rate. Progress of the reaction was followed by disappearance of the bromoketone spot on thin layer chromatography. Additional sodium borohydride is sometimes necessary for complete extinction of the aminoketone starting material. When reaction was complete, the solvent was removed *in vacuo* and the residue suspended in 0.5 liter of $H_2O$ and treated with 4N NaOH to bring about complete solution. This solution was washed well with ether and then the pH was adjusted with acetic acid to pH 8. The resulting mixture was extracted with methylene chloride, the extracts combined and dried ($MgSO_4$) and then concentrated *in vacuo* to give 14.5 g of residual gum.

This gum may be purified by chromatographing on a silica gel column eluting with chloroform-methanol-ammonium hydroxide (90:10:1) to yield 11.6 g of the benzyloxy derivative of compound IV.

The O-benzyl protecting group was removed by hydrogenating a mixture of the O-benzyl derivative of compound IV (11.5 g, 0.02 mole) and 1.8 g of 10% palladium-on-carbon (made wet with absolute ethanol) in 820 mL methanol in a Parr low pressure apparatus. Upon completion of hydrogen take-up, the reduction mixture was filtered and the solid washed with additional methanol. All methanol portions were combined and concentrated to a small volume (approximately 100 mL) and upon standing a white solid gradually precipitated. The solid was isolated by filtration, washed with methanol and dried in air to give 5.6 g material, m.p. 197-198° (61%). This material was dissolved in 40 mL of hot dimethylformamide, filtered and 45 mL $H_2O$ added to the filtrate. Trituration of this solution induced crystallization. Another 10 mL $H_2O$ was added and the mixture was chilled in an ice bath following which the solid was isolated by filtration and washed well with $H_2O$. Drying in air provided 5 g of compound IV, m.p. 197-200° (dec.).

*Example 8*

*N-(2-Hydroxy-5-[1-hydroxy-2-([2-(1H-indol-3-yl)-1,1-dimethylethyl] amino)ethyl] phenyl) methanesulfonamide (Compound IV)*

A solution of 2-(2-amino-2-methylpropyl)indole (X, R=Me; 37.7 g, 0.2 mole) and triethylamine (10.1 g. 0.1 mole) in 1.2 liter of dioxane which had been distilled over sodium metal, was stirred under a nitrogen atmosphere as 5'-bromoacetyl-2'-benzyloxymethane-sulfonanilide (39.8 g, 0.1 mole) was added. The resulting mixture was left stirring for 8-12 hr at approximately 25° under the nitrogen atmosphere. The reaction mixture was filtered, removing some solid precipitate, and the filtrate was treated with a cold solution of sodium borohydride (15 g, 0.4 mole) in 1 liter of absolute ethanol. The borohydride solution was added dropwise to the stirred reaction filtrate. Progress of the reaction was followed by disappearance of the bromoketone spot on thin layer chromatography. Additional sodium borohydride is sometimes necessary for complete extinction of the aminoketone starting material. When reaction was complete, the solvent was removed *in vacuo* and the residue was dissolved in 0.2N NaOH and washed with ether. The pH of this solution was then adjusted with acetic acid to pH 8 and this resulting mixture was extracted with methylene chloride, the extracts combined and dried ($MgSO_4$) and then concentrated *in vacuo* to give the crude O-benzyl derivative of compound V as a residual gum.

The O-benzyl protecting group was removed by hydrogenating a mixture of the O-benzyl derivative of compound V (3.25 g, 0.006 mole) and 1.0 g of $Pd(OH)_2/C$ (Pearlman catalyst) in 100 mL methanol in a Parr low-pressure hydrogenation apparatus. Upon completion of hydrogen take-up, the reduction mixture was filtered and the solid suspended in water and 1N HCl added with warming so that product dissolved. The insoluble catalyst was removed by filtration and the acidic filtrate was made basic (pH 8) with ammonium hydroxide. The resulting precipitate was isolated by filtration, washed with water, and dried in aire to give a nearly quantitive yield of product (compound V) as the monohydrate, m.p. 211-212°.

Anal. Calcd. for $C_{21}H_{27}N_3O_4S \cdot H_2O$: C, 57.92; H, 6.72; N, 9.65; $H_2O$, 4.14
Found: C, 58.05; H, 6.68; N, 9.64; $H_2O$, 3.63.

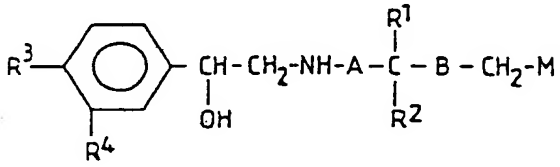
NMR (DMSO-$d_6$): 1.01 (3,s); 1.05 (3,s); 2.75 (4,m); 2.92 (3,s); 4.49 (1,m); 5.30 (6,bs); 7.12 (8,m).
IR (KBr); 740, 1010, 1115, 1125, 1235, 1280, 1460 1500, 1600, and 1610 $cm^{-1}$.
The monohydrate product, obtained above, was converted to the hydrochloride hydrate by dissolution in dilute HCl followed by concentration *in vacuo* to a solid foam, m.p. 105-125°.

Calcd. for $C_{21}H_{27}N_3O_4S \cdot HCl \cdot H_2O$: C, 53.44; H, 6.41; N, 8.91; $H_2O$, 3.82.
Found: C, 53.19; H, 6.37; N, 8.92; $H_2O$, 3.64.

NMR (DMSO-$d_6$): 1.28 (6,s); 2.95 (3,s); 3.17 (4,m); 3.80 (1,bs); 4.90 (1,m); 7.02 (4,m); 7.25 (3,m); 7.60 (1,m); 8.50 (1,bs); 8.78 (1,bs); 9.30 (1,bs); 10.00 (1,bs); 11.10 (1,bs).
IR (KBr): 750, 960, 1150, 1295, 1320, 1400, 1460, 1515, and 1620 $cm^{-1}$.

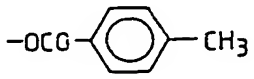
CLAIMS

1. A composition comprising:
(a) an amount effective to produce a topical anti-inflammatory effect of at least one compound, or pharmaceutically acceptable salt or solvate thereof, selected from the group consisting of compounds having the general formula II

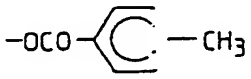


II,

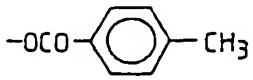
wherein $R^1$ and $R^2$ are independently H or a lower alkyl group, provided that $R^1$ and $R^2$ cannot both be hydrogen;
wherein M is a phenyl group, indole group or hydrogen;
wherein A is the group $(-CH_2-)_n$, in which n is 0, 1, or 2;
wherein B is the group $(-CH_2-)_m$, in which m is the integer 0, 1 or 2;
wherein $R^3$ is either -OH or



and
wherein $R^4$ is either $-NH-SO_2-CH_3$ or



and
(b) a compatible, topically acceptable vehicle for combining said item (a) given above therewith.
2. A composition according to claim 1, wherein m and n are both 0, wherein $R^3$ is -OH, and wherein $R^4$ is $-NH-SO_2-CH_3$.
3. A composition according to claim 2, wherein M is a phenyl group, wherein $R^1$ and $R^2$ are both methyl groups, and wherein m and n are both the integer 0.
4. A composition according to claim 2, wherein M is an indole group, wherein $R^1$ and $R^2$ are both methyl groups, and wherein m and n are both the integer 0.
5. A composition according to claim 2, wherein n equals the integer 0, m equals the integer 0, $R^1$ is a methyl group, $R^2$ is hydrogen, and M is an indole group.
6. A composition according to claim 1, wherein n equals the integer 0, m equals the integer 0, $R^3$ and $R^4$ are both



groups, and M is hydrogen.

7. A method of reducing topical inflammation of a mammal, said method comprising: administering topically to said mammal a nonsteroidal composition comprising a composition according to claim 1, 2, 3, 4, or 5.

8. A composition according to claim 1, wherein said vehicle is a dermatologically acceptable vehicle.

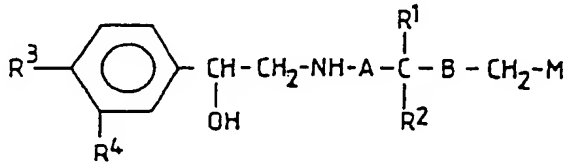
9. A composition according to claim 8, wherein said vehicle is chosen to hinder or reduce systemic absorption of said compound of formula II.

10. A composition according to any of claims 1 to 6, 8 & 9, which is in a cream, lotion or gel.

11. A composition according to any of claims to 1 6, 8 & 9, which is in a spray formulation.

12. A composition according to any of claims 1 to 6, 8 & 9, which is in a suppository formulation.

13. A compound having the formula II



II,

or pharmaceutically acceptable solvate or salt therof, wherein A is $(-CH_2-)_n$ and n is the integer 0 and B is $(-CH_2)_m$ and m is the integer 0 and wherein $R^1$ is $-CH_3$, M is an indole group, $R^3$ is -OH, $R^4$ is $-NH-SO_2-CH_3$, and $R^2$ is selected from the group consisting of H and $-CH_3$.

14. The compound of claim 13 which is 2'-hydroxy-5'-(1-hydroxy-2-[1-(3-indolyl)-2-propylamino]ethyl)-methanesulfonanilide or a pharmaceutically acceptable metal or acid addition salt or hydrate thereof.

15. The compound of claim 13 which is *N*-(2-hydroxy-5-[1-hydroxy-2-([2-(1*H*-indol-3-yl)-1,1-dimethylethyl]amino)ethyl]phenyl)methanesulfonamide or a pharmaceutically acceptable metal or acid addition salt or hydrate thereof.

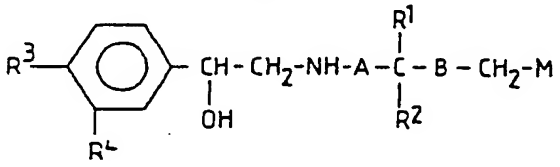
16. A pharmaceutical composition in unit dosage form suitable for systemic administration to a mammal comprising a pharmaceutical carrier and an amount of compound of claim 14 or claim 15 to provide a nontoxic but antiasthmatic effective dose of from 0.1 mcg to 100 mg/kg body weight of said mammal.

17. A pharmaceutical composition comprising a compound of claim 13 admixed in effective antiasthmatic concentration with a suitable propellant system and packaged for aerosol administration.

18. A pharmaceutical composition in form of a powder for insufflation comprising a blend of inert ingredients acceptable for insufflation admixed with a compound of claim 13, said inert ingredients and said compound having appropriate particle size for transport into the bronchioles following insufflation.

19. An antiasthmatic method which comprises administering to a mammalian host having need of such treatment a nontoxic antiasthmatic effective dose of a compound claimed in claim 13.

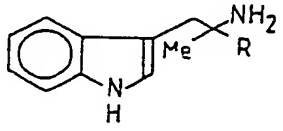
20. A method of preparing a compound of formula II,



II,

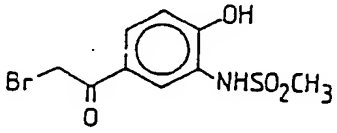
wherein A is $(-CH_2-)_n$ and n is the integer 0 and B is $(-CH_2)_m$ and m is the integer 0 and wherein $R^1$ is $-CH_3$, M is an indole group, $R^3$ is -OH, $R^4$ is $-NH-SO_2-CH_3$, and $R^2$ is selected from the group consisting of H and $-CH_3$, said method comprising:

(a) alkylating an indolylamine of formula X



X,

by a phenolic bromoketone of formula IX



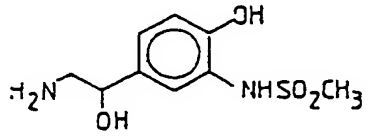
IX,

(b) and then treating the product of step (a) under reaction conditions so as to reduce the carbonyl group to a secondary alcohol, thereby forming said compound of formula II.

21. A method according to claim 20, wherein $R^2$ is H.

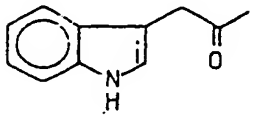
22. A method according to claim 20, wherein $R^2$ is $-CH_3$.

23. A method of preparing a compound of formula II, wherein A is $(-CH_2-)_n$ in which n is the integer 0, wherein B is $(-CH_2)_m$ in which m is the integer 0, and wherein $R^1$ is $-CH_3$, M is an indole group, $R^3$ is -OH, $R^4$ is $-NH-SO_2-CH_3$, and $R^2$ is either H or $-CH_3$, said method comprising:
reacting a compound of formula VIII

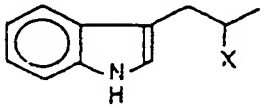


VIII,

with a compound selected from the group consisting of compound (b) and compound (c)



and



(b) (c)

wherein X in (c) is a typical leaving group (for example, halide or tosylate); and wherein when compound (b) is used, reaction conditions are chosen so that reductive amination of compound (b) and reduction take place, so as to form a compound of formula II in which $R^2$ is H; and wherein when compound (c) is used, reaction conditions are chosen so that nucleophilic displacement by compound VIII on compound (c) occurs so as to form said compound of formula II.

24. A method according to claim 20 or 23 substantially as described in any of the foregoing Examples.

25. A compound as claimed in claim 13 prepared by a method according to any of claims 20 to 24.

26. A composition comprising a compound as claimed in claim 25 and a pharmaceutically acceptable vehicle therefor.

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